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# Successful long-term therapy of mucormycosis with isavuconazole

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**ABSTRACT**

We present a case of a 55-year-old poorly controlled diabetic who presented to the hospital with facial pain, ophthalmoplegia, vision changes, and diabetic ketoacidosis and was diagnosed with rhinocerebral mucormycosis due to *Rhizopus microsporus*. He was started on liposomal amphotericin B and micafungin and went for nasal endoscopy and debridement, but the infection had progressed through the base of the skull and he received the maximum tolerated debridement. Posaconazole was added and discontinued due to elevated liver chemistry tests and was replaced with oral isavuconazole. After 6 weeks of therapy with liposomal amphotericin B and isavuconazole, he was switched to oral isavuconazole monotherapy. He underwent 30 sessions of hyperbaric oxygen therapy. Imaging showed improvement with subsequent biopsies that were negative for mucormycosis. At 13 months of therapy, his monotherapy was discontinued. He continues to have long-term sequelae including left facial droop and inability to close his left eye.

**KEYWORDS** Amphotericin; hyperbaric oxygen therapy; isavuconazole; mucormycosis; rhinocerebral mucormycosis; uncontrolled diabetes

Mucormycosis refers to any clinical infection caused by fungi in the order Mucorales. These organisms are found on decaying organic substrates and utilize a spore form to disseminate into the environment.[1] The mortality rate associated with this highly fatal mold is estimated at >50%.[2] Here we describe the fifth known case of mucormycosis successfully treated with isavuconazole therapy.[3–6]

## CASE REPORT

A 55-year-old Hispanic man with a history of diabetes mellitus presented with a 10-day history of worsening left-sided facial pain, swelling, numbness, odontalgia, and diplopia. Initial laboratory evaluation was significant for diabetic ketoacidosis and an elevated hemoglobin A1c (11.4%). By hospital day 2, his acidosis had resolved, but he developed a left-sided cranial nerve VI palsy. Magnetic resonance imaging (MRI) showed extensive inflammation involving the left nasopharyngeal and suprazygomatic masticator space with an asymmetric prominence of the left cavernous sinus suspicious for thrombosis. On day 3, nasal endoscopy with debridement and exploration revealed necrotic mucosa and debris. Mucormycosis was suspected, and he was empirically started on intravenous liposomal amphotericin B (L-AmB) (7 mg/kg). Histopathology revealed broad fungal nonseptate hyphae, and molecular testing was positive for *Rhizopus microsporus*.

In addition to L-AmB, intravenous micafungin was started because data suggest that L-AmB plus echinocandin treatment is associated with improved success in diabetic patients.[1,7] On day 9, posaconazole 400 mg orally twice a day was added and stopped 2 days later due to elevated liver function tests. On day 11, the patient showed decline both clinically (with worsening headaches, vision changes, and facial pain) and by MRI. Salvage therapy with oral isavuconazole was started in addition to L-AmB, and micafungin was discontinued.

Subsequently, two MRIs demonstrated interval progression within the left anterior temporal lobe and along the floor of the middle cranial fossa. Otolaryngology deemed that further debridement was not safe given the risk of

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perforation into the central nervous system. On day 33, the patient was discharged to a long-term acute care facility, where he finished 6 weeks of L-AmB and 5 weeks of isavuconazole before being switched to isavuconazole monotherapy.

At his 11-month follow-up, the patient had evidence of radiographic and endoscopic improvement. He had completed 30 treatment sessions of hyperbaric oxygen therapy and completed 42 weeks of isavuconazole monotherapy. During this period, he tolerated isavuconazole well, with only mild elevation of his liver function tests (~20% above the upper limit of normal). Endoscopic exam showed interval improvement, with biopsies and molecular testing negative for persistent mucormycosis. His blood sugar was well controlled with a hemoglobin A1c of 5.9%. At 13-month follow-up, left facial droop and inability to close his left eye persisted. The patient continues to do well.

## DISCUSSION

To date, the only antifungals approved by the Food and Drug Administration for treatment of mucormycosis are amphotericin and isavuconazole.[2] The approval in 2015 of isavuconazole for invasive fungal infections was largely based on results of the VITAL trial, which proved its noninferiority to L-AmB.[8,9] Recruited patients with proven or probable mucormycosis received isavuconazole as primary therapy. All-cause mortality at day 42 was found to range from 38% to 44%. Patients with refractory disease or those intolerant to prior therapy accounted for the higher mortality (43.7%).[9,10] Similar findings were reported by Marty et al in a matched case-control analysis comparing 21 patients receiving primary treatment with isavuconazole with 33 patients treated with amphotericin; their mortality rates were 33.3% and 41.3%, respectively.[9,10] Compared to posaconazole, isavuconazole has better oral bioavailability, fewer drug-drug interactions, and more favorable pharmacokinetics. In addition, isavuconazole serum concentrations show low intersubject variability, eliminating the need for therapeutic drug monitoring.[11] Therapy appears to be well tolerated, with the most common adverse effects of nausea, vomiting, diarrhea, elevated liver function tests, and hypokalemia.[12]

Recently, the European Confederation of Medical Mycology in cooperation with the Mycosis Study Group Education and Research Consortium published the most comprehensive guideline to date for the diagnosis and management of mucormycosis. In regard to antibiotic therapy, L-AmB continues to be the first-line recommendation for medical management of mucormycosis unless there is preexisting renal compromise, in which case intravenous isavuconazole or intravenous posaconazole is recommended. If the disease continues to progress, the next step is to add isavuconazole or posaconazole. The data are largely based on large case series, and L-AmB has amassed strong clinical data, whereas other treatments do not have such robust data. Monitoring drug levels of isavuconazole does not have supporting evidence but is recommended per guidelines to achieve serum levels >1 μg/mL.[13]

In summary, in cases of rhinocerebral mucormycosis, antifungal therapy should be initiated immediately and surgical evaluation for debridement assessed early and repeatedly. Treatment with isavuconazole should be considered in patients who fail, or are intolerant to, amphotericin therapy, as there is mounting evidence that it results in successful treatment.

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